REMARKS

Upon entry of the foregoing amendment, Claims 15-17, 20-30, 32, 33, and 36-56 will be pending. Applicants have cancelled Claims 1-14, 18, 19, 31, 34 and 35 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability, and reserve the right to pursue the subject matter of the cancelled claims in this or any other patent application. Applicants have amended Claims 15-17, 20-22, 24, 30, 32, 33, and 36-46, and have added new Claims 47-56. The amendments add no new matter and are fully supported by the specification as originally filed. Support for the amendments can be found, for example, on page 8, lines 10-19, page 20, lines 19-23, page 21, lines 5-25, page 43, lines 25-26, page 46, lines 13-22, page 47, lines 8-11, and elsewhere throughout the specification as originally filed.

The Examiner rejected Claims 15-46 in the final Office Action mailed February 11, 2009. Applicants respond below to the specific rejections set forth in the Office Action, as they apply to the presently amended claims. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. § 103(a) –Berg et al. and Kolk et al.

The Examiner has rejected Claims 15-18, 23-29, 32-34, and 39-45 as allegedly being unpatentably obvious over International Patent Application Publication No. WO 02/18635 to Berg et al. ("Berg"), in view of Kolk et al. (1994) *J. Clin. Microbiol.* 32(5):1354-1356 ("Kolk"). The Examiner states that Berg teaches a method for verifying the efficiency of sample preparation of test nucleic acids and the performance of nucleic acid amplification and detection practiced on a test sample after its preparation, by providing an internal control reagent comprising non-viable viral particles, wherein the internal control reagent has an internal control nucleic acid sequence therein, that is an internal control for the release, amplification and detection of a nucleic acid from the test sample. The Examiner argues that Berg teaches the limitations of steps (ii) –(iv) of Applicants' claims, and states that while Berg teaches using non-viable viral particles as an internal control reagent, Berg states that viable cells can be used as internal controls. The Examiner asserts that Berg states that Kolk teaches an internal control reagent that is a genetically engineered viable bacterial cell, used to monitor the efficacy of DNA extraction and the presence of PCR-inhibiting substances. The Examiner argues that as such, it

would have been obvious to use a viable or non-viable internal control as taught by Berg and Kolk, with a reasonable expectation of success.

Applicants respectfully traverse. To establish a *prima facie* case of obviousness, the Examiner must establish that the prior art reference (or references when combined) render all of the claim limitations obvious: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. The Examiner must articulate some reason why the claimed invention would have been obvious, and such reason must be more than a conclusory statement that it would have been obvious. Further, "[a] *prima facie* case of obviousness can be rebutted if the applicant . . . can show 'that the art in any material respect taught away' from the claimed invention." *In re Geisler* 116 F.3d 1465,1469 (Fed. Cir. 1997), quoting *In re Malagrai* 499 F.2d 1297, 1303 (CCPA 1974). As discussed below, the teachings of Berg, either alone or in combination with Kolk, would not reasonably lead the skilled artisan to arrive at the presently claimed invention, and do not render Applicants' presently claimed invention obvious.

In the present application, Applicants discovered that spores can be used as universal internal controls in methods used to verify the efficiency of sample preparation and the performance of nucleic acid amplification and/or detection after sample preparation. In working Examples 2-4 and 6, Applicants describe the purification of spores, and the use of purified spores as an internal control reagent. As described in the instant application, the use of viable internal control reagents provides significant advantages over the use of other internal control reagents, because spores are extremely well-suited for "providing a universal control for microbial cell lysis since bacterial spores are among the most difficult cells to lyse." (Specification, p. 46, lines 4-8).

In contrast to Applicants' presently claimed invention, Berg describes "the use of non-viable particles containing an internal control nucleic acid sequence in nucleic acid-based analysis."(Berg p. 1, lines 4-6). Berg defines a non-viable particle as an "entity which is capable of encapsulating, entrapping or embedding an internal control nucleic acid but which is not capable of propagation either alone (*i.e.*, by self propagation) or by culture in a biological system which would normally allow the propagation of the entity in question." (Berg, p. 18, lines 14-

19). According to Berg, typical non-viable particles are liposomes, protein particles, and viral particles. (Berg, p. 18, lines 20-21 and 28-29).

Not only is Berg completely silent regarding the use of spores as internal control reagents, but the skilled artisan, in view of Berg, would be led away from the use of spores as internal control reagents. Berg notes that non-viable particles provide significant advantages over viable particles, as internal control reagents because they are less laborious and less expensive to make, are biologically active, politically non-controversial, and contain no potential endogenous or exogenous hazardous sequences, such as antibiotic resistance genes. (Berg, p. 5, lines 13-31). Accordingly, in view of the teachings of Berg, one skill in the art would not consider using spores as internal control reagents.

As with Berg, Kolk is completely silent regarding the use of spores as an internal control reagent. Rather, Kolk describes PCR amplification exclusively of *Mycobacterium* sequences. At most, Kolk describes the use of an internal control derived from the same genus to control for PCR amplification. Nothing in Kolk, either alone or in combination with Berg, would render Applicants' presently claimed invention, which relates to methods that utilize spores as a "universal" internal control reagent, obvious.

Applicants' presently claimed invention, which utilizes spores as a universal internal control reagent, is not *prima facie* obvious in view of Berg and Kolk, neither of which indicate that spores can or should be used as a universal internal control reagent. As such, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Rejection Under 35 U.S.C. § 103(a) –Berg et al., Kolk et al., Ke et al., and Kuske et al.

The Examiner has rejected Claims 19-21, 31, and 35-37 as allegedly being unpatentably obvious over Berg and Kolk, in view of Ke et al. (2000) *Clinical Chemistry*, 46(3):324-331 ("Ke") and Kuske et al. (1998) *Appl. Environ. Microbiol.*, 64(7):2463-2472 ("Kuske"). The Examiner's assertions regarding Berg and Kolk are discussed above. The Examiner concedes that neither Berg nor Kolk teaches internal control reagents that are *E. coli* cells or *B. globigii* spores. The Examiner argues that the selection of cells for use in the method is conventional, and represents "routine optimization of reaction components, concentrations, and parameters." (Office Action, at 10). The Examiner asserts that Ke teaches a method of providing an internal

control reagent, "wherein said internal control reagent comprises cells derived from *E. coli*," (*Id.*), and that Kuske teaches an "internal control reagent [that] comprises cells derived from *Bacillus globigii* endospores." (*Id.* at 10-11). The Examiner argues that as such, one skilled in the art would have been motivated to carry out the methods described in Berg and Kuske using different cell types.

Applicants respectfully disagree. As discussed above, Applicants' claimed invention is not *prima facie* obvious in view of Berg and Kolk. The combined teachings of Ke and Kuske do not cure the deficiencies in Berg and Kolk. As discussed in Applicants' Amendment and Response filed August 8, 2007, Ke does not disclose an "internal control reagent [that] comprises cells derived from *E. coli* or bacterial spores," as asserted by the Examiner. Rather, Ke teaches a plasmid that comprises an internal control sequence. The plasmid is purified, isolated, and linearized, and the naked DNA is added into the PCR reaction as an internal control as a PCR assay. Accordingly, Ke does not disclose an internal control reagent that comprises *E. coli* cells or *Bacillus* spores, as suggested by the Examiner. In fact, because the internal control nucleic acids of Ke are purified and isolated prior to addition to the test sample, Ke does not function as a control for nucleic acid extraction, as required by Applicants' claims. Because Ke does not teach the use of cells, *e.g.*, *E. coli*, as an internal control reagent, the Examiner's reliance on Ke, as allegedly teaching the use of cells as internal controls, is misplaced, and Ke is irrelevant to Applicants' claimed invention.

Kuske also does not fill the deficiencies of Berg, Kolk and Ke. The Examiner asserts that Kuske teaches an internal control reagent comprising *Bacillus globigii* endospores isolated from an environmental sample. As discussed in Applicants' Amendment and Response filed August 8, 2007, Kuske does not teach using *B. globigii* spores as an internal control reagent. In fact, Kuske is completely silent regarding internal controls. At most, Kuske teaches a method to determine the detection limit of *B. globigii* cells from a soil sample, comprising seeding *B. globigii* cells in soil, preparing nucleic acids from the soil sample, and amplifying *B. globigii* nucleic acids. Accordingly, the teachings of Kuske add nothing to the teachings of Berg, Kolk, and Ke, and none of the references render the use of spores as an internal control reagent obvious.

In view of the foregoing, Berg, Kolk, Ke and Kuske fail to support a *prima facie* case of obviousness under 35 U.S.C. § 103(a). Applicants respectfully request reconsideration and withdrawal of the rejection accordingly.

Rejection Under 35 U.S.C. § 103(a) –Berg et al., Kolk et al., and Piccard et al.

The Examiner has rejected Claims 30 and 46 as allegedly being unpatentably obvious over Berg and Kolk, in further view of Picard and Bergeron (2002) *Drug Disc. Today*, 7(2):1092-1101 ("Picard"). The Examiner's assertions regarding Berg and Kolk are discussed above. The Examiner concedes that neither Berg nor Kolk teaches a sample preparation procedure that includes the steps of nucleic acid extraction and elimination, neutralization and inactivation of nucleic acid testing (NAT) inhibitors. The Examiner alleges that Berg teaches each and every limitation of Claims 30 and 46 but does not teach a sample preparation procedure comprising the steps of nucleic acid extraction and elimination, neutralization and/or inactivation of nucleic acid testing (NAT) inhibitors, which Picard teaches. Applicants respectfully traverse.

Applicants note that claims 30 and 46 ultimately depend from independent Claim 15. Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness or that Berg and Kolk disclose the invention of Claims 15 as amended, for at least the reasons discussed above. Thus, even if Picard did teach nucleic acid extraction and elimination, neutralization and inactivation of NAT inhibitors, a point Applicants do not concede, the addition of these elements to Berg does not cure the deficiencies of Berg noted above.

Applicants therefore respectfully request that, for at least these reasons, the PTO reconsider and withdraw the rejection of Claims 30 and 46 as obvious over Berg and Kolk in light of Picard.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other

broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: July 29, 2009

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